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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 10/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/071,510	CLARK ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2004 and 23 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-69* is/are pending in the application.

4a) Of the above claim(s) *2,3,9,10 and 15-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-8 and 11-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The supplemental election without traverse filed June 23, 2005 is acknowledge and has been entered.

In responding the additional restriction and election requirement set forth in the Office action mailed March 23, 2005 Applicant has elected the species of the invention of Group I, wherein said agent is a combination of agents consisting of a taxane compound and a platinum compound.

2. The election filed June 29, 2004 is acknowledged and has been entered.

In responding the restriction and election requirement set forth in the Office action mailed May 3, 2004 Applicant has elected the invention of Group I, claims 1-14, drawn to a method for determining whether an agent can be used to reduce the growth of a tumor, wherein said method comprises obtaining a sample of tumor cells and determining whether the tumor cells express one or more sensitivity markers. In addition, Applicant has elected the species of the invention of Group I, wherein said one or more sensitivity marker is SEQ ID NO: 16.

Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 1-69 re pending in the application. Claims 2, 3, 9, 10, and 15-69 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention or species of invention, there being no allowable generic or linking claim. Election was made **without** traverse in the replies filed on June 29, 2004 and June 23, 2005.

4. Claims 1, 4-8, and 11-14 are currently under prosecution.

Oath/Declaration

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: It was not executed in accordance with either 37 CFR 1.66 or 1.68.

Specification

6. The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified. Reference to hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified is impermissible and therefore requires deletion.

An example of such impermissible disclosures appears at page 25, line 37, of the specification.

The attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP § 608.01(p), paragraph I regarding acceptable incorporation by reference. See 37 CFR § 1.57.

7. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of such an improperly demarcated trademark is Microsoft™ (page 63, line 36).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate

symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

Claim Objections

8. Claims 1, 4-8, and 11-14 are objected to as being drawn to the subject matter of non-elected species of invention; however, at this time, it is not necessary that this issue be remedied.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 5, 6, 12, and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5, 6, 12, and 13 are indefinite because the claims recite, "wherein the level of expression is determined by detecting [...]". Claims 1 and 8 do not recite a step comprising determining the level of expression of the marker, as they only include a step comprising determining whether the tumor cells express the marker. Accordingly, there is no antecedent basis in claims 1 and 8 to support these recitations in claims 5, 6, 12, and 13. Therefore, the metes and bounds of the subject matter that Applicant regards as the invention has not been set out with the requisite degree of clarity and particularity to permit the skilled artisan to recognize infringing subject matter.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1, 4-8, and 11-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

The claims are drawn to a method for determining whether an agent can or cannot be used to reduce the growth of a tumor comprising determining the presence, or the level of expression of one or more markers.

The term "marker" is defined at page 4 of the specification to mean a nucleic acid molecule corresponding to a polynucleotide sequence, which in this instance is the species of marker identified as SEQ ID NO: 16. According to the definition provided, the term is meant to include, for example, a messenger RNA (mRNA) and a gene (i.e., a genomic DNA molecule comprising introns and exons, which is transcribed to yield a messenger RNA (mRNA) molecule corresponding to the sequence set forth as SEQ ID NO: 16).

The term "agent" is defined broadly as "anything that cancer cells, including tumor cells, may be exposed to in a therapeutic protocol" (page 10, lines 12-21). Thus, it is evident that the term "agent" includes any compound or any combination of a multitude of compounds that may have be used to reduce the growth of a tumor.

The specification discloses, "cancer cells, including tumor cells, refer to cells that divide at an abnormal (increased) rate" (page 13, lines 10 and 11).

The term "taxane compound" is defined at page 66, lines 7-10, to include Taxol™, compounds which are structurally similar to Taxol™ and/or analogs of Taxol™, and "mimics" (i.e., compounds which may not be structurally similar to Taxol™ but mimic the therapeutic activity of Taxol™ or structurally similar taxane compounds *in vivo*).

The term "platinum compound" page 70, lines 2-7, to include cisplatin, compounds which are structurally similar to cisplatin, as well as analogs and derivatives of cisplatin, and "mimics" (i.e., compounds which may not be structurally similar to cisplatin but mimic the therapeutic activity of cisplatin or structurally related compounds *in vivo*).

The Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

"[G]eneralized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

The specification describes ovarian cancer specimens expressing various markers as being described by clinicians as resistant or susceptible to a combination of Taxol™ (paclitaxel) and cisplatin; see, e.g., page 65, lines 10-37; and Tables 1-6. The cancer cells' sensitivity to this combination of therapeutic agents is attributed to the presence of one or more of these various markers, including a marker corresponding to the polynucleotide sequence identified as SEQ ID NO: 16 (Tables 2A and 5). On the other hand, the cancer cells' insensitivity to this combination of agents is attributed to the lack of, or the underexpression of these various markers. The specification also describes other markers whose presence or level of expression is correlated with the cancer cells' resistance to this combination of agents.

In contrast, the claims are directed to a method for determining whether any member of a genus of structurally and functionally different agents can or cannot be

used to reduce the growth of any members of a genus of etiologically and pathologically distinct tumor cells, wherein said method comprises obtaining a sample of tumor cells, determining whether the tumor cells express one or more markers, wherein at least one of said markers is a marker corresponding to the polynucleotide sequence of SEQ ID NO: 16

In this instance, there is no language that adequately describes at least a substantial number of the members of the structurally and functionally disparate agents to which the claims are directed. A description of what a material does, or might do, rather than of what it is, does not suffice to describe the claimed invention.

It is aptly noted that the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, i.e., the ability to reduce the growth of a tumor, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1894 (CAFC 2004). The claimed method depends upon finding agents that might be used to reduce the growth of a tumor; moreover, it depends upon finding agents

whose ability to reduce the growth of tumor cells expressing one or more particular markers is known or determinable as correlating with the presence or level of expression of those one or markers; and without such agents, it is impossible to practice the invention.

Although the skilled artisan could potentially practice the claimed invention by identifying or selecting agents that might be used for reducing the growth of a tumor and then determining whether the claimed invention can be practiced using that agent by determining if there is a correlation between the presence and/or level of expression of a marker corresponding to the nucleic acid sequence of SEQ ID NO: 16 and the sensitivity of a given sample of the tumor to the agent, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for enabling it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims are directed to a genus of agents having the ability to reduce the growth of tumor cells, which vary both structurally and functionally, an

adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

Absent the adequate description of a representative number of members of the genus of agents to which the claims are directed, the supporting disclosure amounts to no more than a mere invitation to identify or select a substance that might be used as an agent for reducing the growth of a tumor and then determining whether the claimed invention can be practiced using that agent by determining if there is a correlation between the presence and/or level of expression of a marker corresponding to the nucleic acid sequence of SEQ ID NO: 16 and the sensitivity of a given sample of the tumor to the agent.

Because the claims are directed to a method for determining whether an agent can or cannot be used to reduce a tumor by determining the presence, or level of expression of one or more markers, it is recognized that to practice the invention it is necessary to know beforehand, or to first establish that a correlation exists between the presence or level of expression of these one or more markers and the sensitivity or insensitivity of the tumor cells to a selected agent. Unless such a correlation has already been established, doing so requires not only prior possession of the agent, but also prior possession of the tumor, or perhaps a cell line derived from the tumor.

Here, the specification merely describes the correlation of one or more markers, including a marker identified by the nucleotide sequence set forth as SEQ ID NO: 16 and the sensitivity of ovarian cancer cells to the combination of Taxol™ (paclitaxel) and cisplatin. No other correlation between the expression of these one or more markers

and the sensitivity, or lack thereof, of any other type of cancer to any other agent has been described.

While this disclosure might be considered to provide *in ipsis verbis* support for the claimed invention, because the specification includes no other description of such a correlations, which must be known or established before the invention can be practiced.

The Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

See also: University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

It is submitted that to adequately describe the claimed invention, it would be necessary to describe correlations between the presence and/or levels of expression of one or more adequately described markers in at least a representative, or substantial number of different types of tumors and their sensitivity, or lack thereof, to at least a representative number of members of the genus of agents to which the claims are directed. While the specification describes a correlation between the presence of one or more adequately described markers in ovarian cancer cells and their sensitivity or lack thereof to a combination of Taxol™ (paclitaxel) and cisplatin, it would not suffice to adequately describe the claimed invention, such as to reasonably convey to the skilled artisan that Applicant had possession of that invention at the time the application was filed. This is because, in part, ovarian cancer cells are not representative of the whole of the genus of tumors to which the claims are directed. Because of etiologic and pathologic differences, the presence of one or more markers in different members of the genus of tumors may not always correlate with their sensitivity to an agent. Furthermore, the combination of Taxol™ and cisplatin is not representative of the whole

of the genus of agents to which the claims are directed. Because of the different structures, specificities, modes of action, additive and/or synergistic effects of different agents, the presence of one or more markers in any given tumor may not always correlate with its sensitivity to the agents.

Furthermore, it is aptly noted that the specification does not describe a genomic DNA molecule (i.e., a gene) corresponding to the nucleotide sequence identified as SEQ ID NO: 16. A description of the nucleotide sequence of a complementary DNA (cDNA) molecule derived from a transcript (i.e., messenger RNA (mRNA) molecule), such as the nucleotide sequence of SEQ ID NO: 16 does not suffice to describe the structure of a corresponding gene, and particularly the structure of the introns of which the gene is comprised, as the mRNA molecule contains no information that could be used to glean the structure of either the introns or the gene. Given the definition of the term "marker", as recited in the claims, absent a detailed description of the gene corresponding to the nucleotide sequence of SEQ ID NO: 16, the disclosure would not reasonably convey Applicant's possession of the claimed invention at the time the application was filed.

In addition, the specification discloses the nucleotide sequence of SEQ ID NO: 16 is novel and does not teach whether the nucleotide sequence encodes all or part of a protein. Yet, claims 6 and 13 are specifically directed to methods comprising determining whether tumor cells express one or more markers, including a marker corresponding to the nucleotide sequence of SEQ ID NO: 16 by detecting and quantifying the amount of protein that is encoded by those markers. Absent a description of the protein encoded by those markers, and particularly of the protein encoded by a marker corresponding to the nucleotide sequence of SEQ ID NO: 16, the disclosure would not reasonably convey Applicant's possession of the claimed invention at the time the application was filed.

13. Claims 1, 4-8, and 11-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue experimentation.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

For reasons explained above in the written description rejection, the claims are directed to a method for determining whether any member of a genus of structurally and functionally different agents can or cannot be used to reduce the growth of any members of a genus of etiologically and pathologically distinct tumor cells, wherein said method comprises obtaining a sample of tumor cells, determining whether the tumor

cells express one or more markers, wherein at least one of said markers is a marker corresponding to the polynucleotide sequence of SEQ ID NO: 16

Here, the specification merely describes the correlation of one or more markers, including a marker identified by the nucleotide sequence set forth as SEQ ID NO: 16 and the sensitivity of ovarian cancer cells to the combination of Taxol™ (paclitaxel) and cisplatin. No other correlation between the expression of these one or more markers and the sensitivity, or lack thereof, of any other type of cancer to any other agent has been described.

The claimed method depends upon making and/or finding agents that might be used to reduce the growth of a tumor; moreover, it depends upon making and/or finding agents whose ability to reduce the growth of tumor cells expressing one or more particular markers is known or determinable as correlating with the presence or level of expression of those one or markers; and without such agents and without such tumor cells, it is impossible to practice the invention, because it would not be possible to establish a correlation between the presence or level of expression of one or more markers in the tumor cells and their sensitivity to the agents.

Before the skilled artisan could use the claimed invention, it would be necessary to determine whether correlations exist between the presence and/or levels of expression of one or more adequately described markers in at least a representative, or substantial number of different types of tumors and their sensitivity, or lack thereof, to at least a representative number of members of the genus of agents to which the claims are directed. Therefore, while the specification teaches a correlation between the presence of one or more adequately described markers in ovarian cancer cells and their sensitivity or lack thereof to a combination of Taxol™ (paclitaxel) and cisplatin, this amount of guidance, direction, and exemplification is not reasonably commensurate in scope with the breadth of the claims and would not be sufficient to enable the skilled artisan to use the claimed invention without undue and unreasonable experimentation.

There are many reasons the disclosure would not be sufficient to enable the skilled artisan to use the claimed invention without undue and unreasonable experimentation. These reasons include the fact that ovarian cancer cells are not

representative of the whole of the genus of tumors to which the claims are directed. Because of etiologic and pathologic differences, the presence of one or more markers in different members of the genus of tumors may not always correlate with their sensitivity to an agent. Furthermore, the combination of Taxol™ and cisplatin is not representative of the whole of the genus of agents to which the claims are directed. Because of the different structures, specificities, modes of action, additive and/or synergistic effects of different agents, the presence of one or more markers in any given tumor may not always correlate with its sensitivity to the agents. As such, the existence of such correlations cannot be predicted or known beforehand, but only determined empirically.

These conclusions are supported by the teachings of Abuharbeid et al. (*Naunyn-Schmidedberg's Arch. Pharmacol.* 2005; **371**: 141-151), for example. Abuharbeid et al. teaches that overexpression of HER-2 in breast cancer cell lines can confer resistance to paclitaxel; see entire document (e.g., page 142, column 1). However, for ovarian carcinoma cells, Abuharbeid et al. teaches there is conflicting data (page 142, column 1). Abuharbeid et al. discloses that reduction of HER-2 expression in a Her-2-overexpressing ovarian carcinoma cell line leads to increased resistance to paclitaxel, an observation which is at odds with the effect of its overexpression in breast cancer cell lines (page 142, column 2); yet, in another ovarian cancer cell line, a reduction in HER-2 expression led to increased sensitivity to the drug (page 142, paragraph bridging columns). These observations led Abuharbeid et al. to perform a study comparing the effects of inhibiting the expression of HER-2 by three independent targeting strategies upon the sensitivity of an ovarian cancer cell line to paclitaxel; they found that each of the different means by which HER-2 expression was inhibited led to different effects upon the cells' sensitivity to the drug (e.g., the abstract). Thus, the teachings of Abuherbeid et al. underscore the unpredictable nature of the art of determining the sensitivity or insensitivity of cancer cells to an agent by determining and comparing the level of expression of a marker.

It is nevertheless feasible that a gene expression profile may be determined which identifies particular types of cancer that are sensitive, or not, to particular agents or combinations of agents. For example, Ayers et al. (*J. Clin. Oncol.* 2004 Jun 15; **22**

(12): 2284-2293) concludes that transcriptional profiling has at least the potential to be used to identify a gene expression pattern in breast cancer that may lead to clinically useful predictors of pathologic complete response to certain neoadjuvant combinatorial therapy; see entire document (e.g., the abstract). Even so, Ayers et al. concludes that their study revealed no single marker sufficient associated with pathologic complete response to be used as an individual predictor (abstract).

Although the specification asserts that a correlation exists between one or more of the disclosed markers, including a marker identified by the nucleotide sequence set forth as SEQ ID NO: 16 and the sensitivity of ovarian cancer cells to the combination of Taxol™ (paclitaxel) and cisplatin, the use of the claimed invention to determine whether an agent can or cannot be used to reduce the growth of a tumor has not been exemplified. Although the specification discloses statistical algorithms were used to establish the correlation (page 65), the algorithms and methodology used in the analyses performed have not been described, such that it would be possible to repeat such analyses using other agents and other types of tumors.

In accordance with claim 1, the mere presence of one or more markers in the tumor cells identifies the cells as having sensitivity to the agent, such that the agent may be used to reduce the growth of the tumor cells. In contrast, according to claim 8 is it not just the mere presence of one or more markers, but rather their complete absence or their relatively lower abundance that identifies the cells as not having sensitivity to the agent. Why is that the absence or underexpression of the one or more markers and the tumor cells' insensitivity to an agent are inversely correlated, whereas it is merely the presence of the marker, rather than its overexpression that allegedly positively correlates with the tumor cells' sensitivity to the agent? In practicing the invention of claim 1, if the markers are present, the tumor cell is identified as sensitive to the agent; it would follow logically that if the markers are not present, the tumor cell is identified as lacking sensitivity to the agent. Yet, in practicing the invention of claim 8, it paradoxically seems that the mere presence of the markers in the tumor cells fails to identify the cells as having sensitivity to the agent, as instead tumor cells that underexpress the markers are identified as lacking sensitivity.

With particular regard to the marker corresponding to the nucleic acid sequence set forth as SEQ ID NO: 16, the specification teaches only that it is a marker of sensitivity, as opposed to a marker of resistance. The specification fails to teach whether it is the mere presence of such markers, or their relative levels of expression that correlate with tumor cells' sensitivities to agents. If it the level of expression of the markers, rather than their mere presence, that identifies a tumor cell has having sensitivity to an agent, it is duly noted that the specification provides insufficient guidance and direction to use the claimed invention without undue and unreasonable experimentation, since, for example, the disclosure does not provide a description of the standard to which such comparisons of the levels of expression are to be made. When is the marker underexpressed? How does one determine if it is underexpressed, when there is no standard for ascertaining whether it is underexpressed?

Further regarding claims 1 and 8, while the specification discloses a correlation between the sensitivity of ovarian cancer cells to a combination of paclitaxel and cisplatin and the presence, or level of expression of one or more markers in those cells, it does not show a correlation between the sensitivity of the cells to either paclitaxel or cisplatin alone, or any other drug or combination of drugs. It is submitted that because each different drug in a given combination has, for example, a discrete mode of operation, and because the drugs may have additive or synergistic, or counteractive effects upon the growth of particular tumor cells, it is submitted that it is not possible to extrapolate the data presented in this application to reliably predict the effects of the different drugs alone.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Conclusion

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

slr
September 19, 2005